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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2015) 1-8

Alzheimer's & Dementia

A systematic review and meta-analysis of retinal nerve fiber layer change in dementia, using optical coherence tomography

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Abstract

Introduction: Retinal nerve fiber layer (RNFL) thinning, assessed by optical coherence tomography (OCT), has recently been reported in various dementias.

Methods: We conducted a systematic review and meta-analysis to investigate the diagnostic utility of RNFL thickness measurement using OCT in dementia (including Alzheimer's disease [AD] and mild cognitive impairment [MCI]) compared with healthy controls (HC).

Results: Seventeen studies comparing AD with HC (702 AD eyes and 790 HC eyes) were included, demonstrating a significant reduction in mean RNFL thickness in AD (weighted mean difference [WMD] 12.44, 95% confidence interval or CI [−16.64, −8.25], P <.0001). Five studies comparing MCI and HC (214 MCI eyes and 421 HC eyes) were included demonstrating a significant reduction in mean RNFL thickness in MCI (WMD −8.23, 95% CI [−14.00, −2.45], P =.005). No relevant studies were identified for other dementias.

Discussion: OCT measurement of RNFL thickness appears diagnostically useful in discriminating between AD, or MCI, and HC.

Keywords: OCT; Alzheimer's disease; Dementia; Mild cognitive impairment; Optical coherence tomography; Retinal imaging

1. Introduction

Pathological changes in the eye have recently been reported in a range of neurodegenerative diseases. The retina is essentially an extension of the brain, and shares embryological origins with regions responsible for cognition [1]. Visual symptoms, including impaired visual fields and acuity are commonly reported in early Alzheimer's disease (AD) [2]. Optical coherence tomography (OCT) is a noninvasive, noncontact optical scanning method, for cross-sectional imaging of the internal retinal structure. As a clinical imaging device, the operation is straightforward and patient satisfaction is extremely high thanks to its fast acquisition (just a few seconds) and noncontact scan. Advancements in the technology of the light source and detector in recent years now permit extremely detailed visualization and precise measurement of the retinal layers, including the retinal nerve fiber layer (RNFL). The RNFL consists of the unmyelinated axons of the retinal ganglion cells, which together form the optic nerve and anterior visual pathways [3]. Measurement of the RNFL thickness in the retina is therefore a measurement of axonal loss in the anterior visual pathways.

Thinning of the RNFL has been described in a range of neurological disorders including multiple sclerosis [3], Parkinson's disease [4], and neuromyelitis optica [4]. Recently, RNFL thinning in patients with AD [4–13] and mild cognitive impairment (MCI) [11,12,14] have also been reported.

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http://dx.doi.org/10.1016/j.dadm.2015.03.001

RNFL thinning in AD has been hypothesized to occur because of retrograde degeneration of the retinal ganglion cell axons [9], and these changes have been suggested to occur even before memory is affected [15]. There is also a suggestion that neuroretinal atrophy may occur as a result of amyloid-β plaque deposits within the retina, although this hypothesis remains more speculative [7].

We aimed to conduct a systematic review and meta-analysis of the literature to determine the diagnostic utility of OCT measurement of the RNFL thickness in various dementias, including AD, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia (VaD), and MCI.

2. Methods

2.1. Search strategy and study selection

We systematically searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Excerpta Medica Database (EMBASE) via OVID for all human studies published until September 2014, in all languages. The Medical Subject Heading (MeSH) search terms used were: (1) "dementia", (2) "Alzheimer disease", (3) "dementia, vascular", (4) "dementia, multi-infarct", (5) "Lewy body disease", (6) "mild cognitive impairment", and (7) "tomography", (8) "tomography, optical coherence", and (9) "OCT". We searched Web of Knowledge, Scopus, and Google Scholar for all studies published before and including September 2014 using the MeSH terms: (1) "optical coherence tomography", (2) "OCT", and (3) "dementia", (4) "Alzheimer", (5) "mild cognitive impairment", and (6) "MCI". Further studies were identified through reference and citation searching of relevant articles, and hand-searching of relevant journals.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: (1) original study; (2) study of diagnostic utility of OCT; (3) diagnosis of dementia based on appropriate criteria for the diagnosis of AD, such as the National Institute of Neurological, Communicative Diseases and Stroke and Alzheimer's Disease and Related Disorders Association [16]; (4) diagnosis of AD, FTD, DLB, VaD, or MCI; (5) comparison of RNFL thickness in patients versus control; (6) total subjects in the study of at least 10; and (7) age and sex-matched control group.

We excluded the following studies: (1) review articles; (2) abstract-only studies; (3) case reports; and (4) studies of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy dementia.

2.3. Data extraction

We initially screened all studies identified in the systematic search of the online databases by abstract and title. Irrelevant or duplicate studies were removed, and the remaining articles were assessed for eligibility by full-text review. Data extracted from these studies included: title; authors; center; publication year; aim of study; study type; disease focus; number of patients and controls; characteristics of patients including male:female ratio, mean age, and participant selection criteria; diagnostic criteria; method of OCT used; and results and authors' suggestions.

2.4. Quality assessment

We assessed all full-text studies included in data analysis using the Quality Assessment for Diagnostic Accuracy Studies tool to determine the risk of bias and variability in each study [17].

2.5. Statistical analysis

We extracted original data from the studies (means, standard deviations, sample sizes) and where required calculated data which were not available. We used RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) [18] for the meta-analysis of these continuous outcomes, calculating the summary estimates including 95% confidence intervals (CIs). We used the means, standard deviations, and sample sizes extracted from the studies to calculate the weighted mean difference (WMD) using the inverse-variance random-effects model. A P value of less than .05 was considered to be statistically significant. To assess heterogeneity, we used the chi-squared test, tau-squared, and the Higgins I^2 test, with an I^2 value of more than 50% being significantly heterogeneous. We performed subgroup analysis according to the type of OCT used and whether one or both eyes were used per subject. We also performed sensitivity analysis to further evaluate the heterogeneity by excluding studies where the required data had to be calculated from the data provided. We used funnel plot to assess for possible publication bias.

3. Results

Five hundred and fifty-five studies were identified in the literature search, with a further three identified through citation searching and hand-searching. Two hundred and thirty-six were duplicates and therefore removed, leaving 322 studies which were screened by abstract and title only; 288 were deemed ineligible at this stage, and a further eight studies were excluded as these were abstract only conference presentations. Seven studies were removed; three were deemed ineligible after full text review as they did not measure the RNFL, one study was a duplicate, another study did not compare RNFL thickness in patients to controls, and two studies reported insufficient data for analysis. Nineteen articles were therefore eligible; 17 compared AD to controls (totalling 702 AD eyes and 790 control eyes) with 5 studies comparing MCI to controls (totalling 214 MCI eyes and 421 control eyes); 3 of these 19 studies compared both AD and MCI.

Thirteen studies determined the RNFL thickness in patients with AD compared with healthy controls (HC), seven

of which used spectral domain OCT (SD-OCT) and six used time domain (TD-OCT). Eleven articles reported the mean overall RNFL thickness (Table 1 and Fig. 1), and 11 also reported the RNFL thickness by quadrant (superior, inferior, temporal, and nasal) (Table 2). Three articles also compared the overall RNFL thickness in patients with MCI compared with controls (Table 3 and Fig. 2), and two of these articles reported RNFL thickness by quadrant (Table 4). No eligible studies determined the RNFL thickness in patients with FTD, DLB, or VaD.

3.1. RNFL thickness in AD patients compared with controls

We identified a total of 17 studies including 702 AD eyes and 790 control eyes. There was a significant reduction in the overall mean RNFL thickness in AD patients compared with controls (WMD −12.44, 95% CI [−16.64, −8.25], P <.0001) (Table 1, Fig. 1). We identified 14 studies including 588 AD eyes and 698 control eyes assessing the mean RNFL thickness by quadrant, all of which demonstrated significant reduction in patients with AD compared with HC; superior quadrant (WMD −17.07, 95% CI [−25.26, −8.89], P <.0001); inferior (WMD −16.62, 95% CI [−24.48, −8.76], P <.0001); temporal (WMD −8.71, 95% CI [−13.66, −3.76], P =.0006); and nasal (WMD −9.35, 95% CI [−14.33, −4.38], P =.0002) (Table 2, Appendix A).

Significant heterogeneity was identified between the studies, with values of heterogeneity for overall mean RNFL thickness of tau^2 67.27, chi^2 377.84, df 16 (P <.00001), and I^2 96%. Therefore we further evaluated the studies by performing subgroup analysis and sensitivity analysis (Appendix C). We performed two subgroup analyses: (1) type of OCT used (TD-OCT or SD-OCT), (2) one or both eyes used per subject (excluding studies where a mix of one and both eyes were used). In the subgroup analysis according to the type of OCT used, there were 7 TD-OCT studies and 10 SD-OCT studies for the overall mean RNFL thickness, and 6 TD-OCT and 8 SD-OCT studies for the RNFL thickness by quadrant. There were statistically significant reductions in the overall, inferior and temporal RNFL thickness regardless of whether TD-OCT or SD-OCT was used. The TD-OCT studies showed a larger weighted mean difference for the overall mean RNFL thickness compared with the SD-OCT studies (TD-OCT WMD −20.89, 95% CI [−29.32, −12.45], P <.00001; SD-OCT WMD −6.92, 95% CI [−11.66, −2.18], P =.004). We also further analyzed the TD-OCT and SD-OCT studies based on the OCT model used. Heterogeneity became nonsignificant within the Spectralis and Cirrus model analysis, but was still present within the other models.

In the subgroup analysis according to one or both eyes used per subject, there were seven studies each for the overall mean RNFL thickness, and seven "one eye" studies and five "both eyes" studies for the RNFL thickness by quadrant. There were statistically significant reductions in the overall, superior and inferior RNFL thickness regardless of whether one or both eyes were used. In the sensitivity analysis, we excluded the studies where the required data had to be calculated from

Table 1
AD vs. normal controls: overall RNFL thickness

Study	OCT type	One or both eyes	Number of subjects (eyes)		Mean age ± SD (yrs)		Overall mean RNFL thickness ± SD (μm)	
			AD	Controls	AD	Controls	AD	Controls
Ascaso et al. [9]	TD	Both	18 (36)	41 (82)	AD and MCI: 72.1 ± 8.7	72.9 ± 7.9	64.96 ± 16.71***	103.1 ± 8.04
Berisha et al. [14]	TD	One	9 (9)	8 (8)	74.3 ± 3.3	74.3 ± 5.8	85.5 ± 7.4	93.8 ± 10.4
Chi et al.[19]	TD	One	12 (12)	17 (17)	75.39 ± 7.30	75.29 ± 5.84	93.18 ± 11.36	99.44 ± 8.88
Garcia-Martin et al. [15]	SD	One	20 (20)	28 (28)	79.3 ± 4.1	72.1 ± 5.1	88.6 ± 20.5	89.2 ± 20.9
Gharbiya et al. [20]	SD	Both	21 (42)	21 (42)	73.1 ± 6.9	70.3 ± 7.3	96.8 ± 6.9	95.9 ± 8.5
Günes et al. [5]	SD	One	40 (40)	40 (40)	75.02 ± 6.34	74.15 ± 5.76	84.0 ± 7.0***	107.1 ± 6.3
Iseri et al. [12]	TD	Both	14 (28)	15 (30)	70.16 ± 9.7	65.1 ± 9.8	87.46 ± 23.78***	113.16 ± 6.72
Kang et al. [8]	SD	Both	8 (16)	8 (16)	71.5	67.4	80.44 ± 16.73*	92.50 ± 9.8
Kesler et al. [10]	TD	Mix	30 (52)	24 (38)	73.7 ± 9.9	70.9 ± 9.2	84.7 ± 10.6*	94.3 ± 11.3
Kirbas et al. [7]	SD	Both	40 (80)	40 (80)	69.3 ± 4.9	68.9 ± 5.1	65.0 ± 6.2***	75.0 ± 3.8
Kromer et al. [21]	SD	Mix	22 (42)	22 (42)	75.9 ± 6.1	64.0 ± 8.2	105 ± 17.0	101.8 ± 10.7
Larrosa et al. [22]	SD	One	151 (151)	61 (61)	75.29	74.87	97.55 ± 14.12	100.55 ± 12.99
Moreno-Ramos et al. [23]	SD	Both	10 (20)	10 (20)	73.0 ± 6.5	70.2 ± 5.5	94.5 ± 2.2***	108.0 ± 2.2
Paquet et al. [11]	TD	Both	26 (52)	15 (30)	78.5 ± 4.91	75.5 ± 5.1	83.4 ± 7.19**	102.2 ± 1.8
Parisi et al. [13]	TD	One	17 (17)	14 (14)	70.37 ± 6.1	Age-matched	59.5 ± 16.7**	99.9 ± 8.95
Polo et al. [6]	SD	One	75 (75)	75 (75)	74.15 ± 9.15	73.98 ± 9.05	97.40 ± 11.2	99.21 ± 9.9
Zhu et al. [24]	SD	NR	10 (NR)	167 (NR)	79.6 ± 8.6	75.5 ± 7.7	90.7 ± 15.8***	96.7 ± 9.6

Abbreviations: AD, Alzheimer's disease; RNFL, retinal nerve fiber layer; OCT, optical coherence tomography; SD, standard deviation; TD, time-domain; SD, spectral domain; NR, not reported.

NOTE. One or both eyes or a mix of one and both eyes used per subject in the evaluation of mean RNFL thickness. Number of subjects (number of eyes in brackets).

*P < 0.05, **P < 0.01, ***P < 0.001.

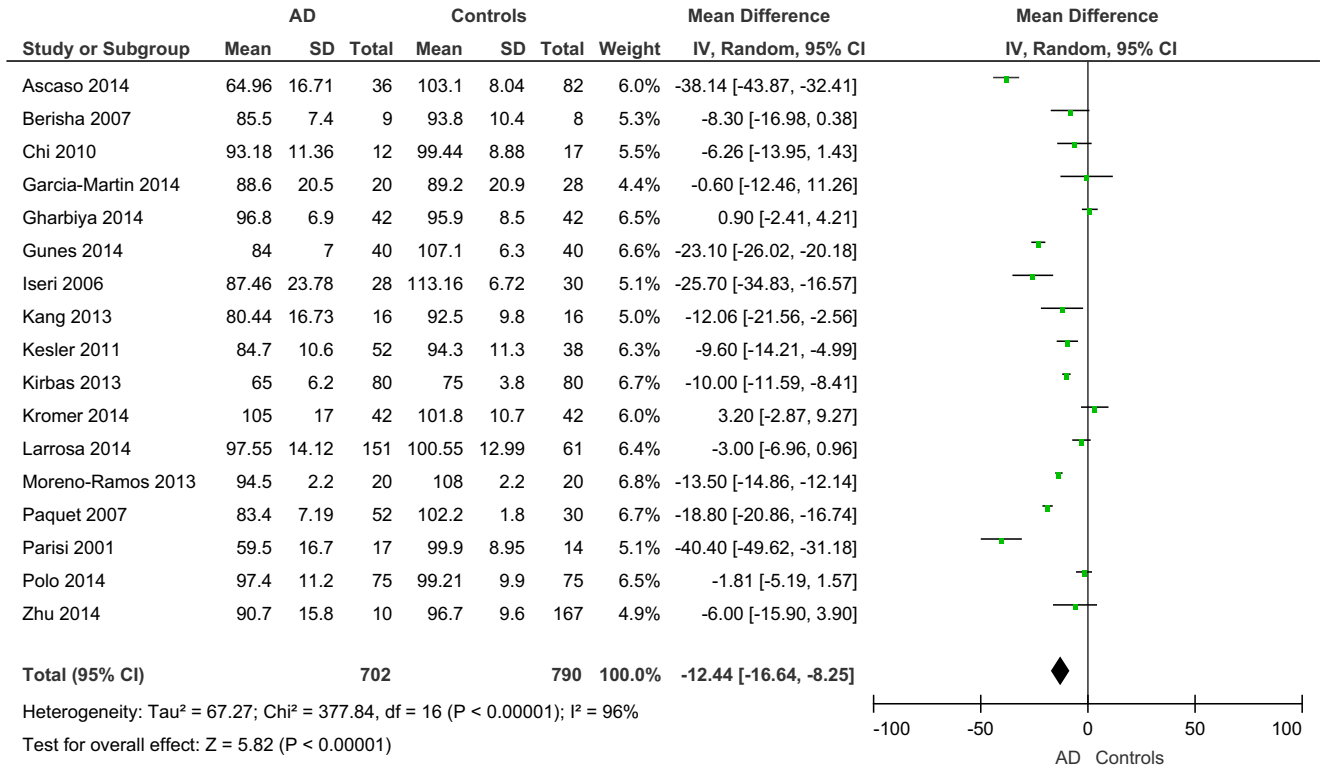

Fig. 1. Meta-analysis of Alzheimer's disease (AD) vs. normal controls: overall retinal nerve fiber layer (RNFL) thickness.

the data provided (Ascaso et al. [9], Berisha et al. [14], Garcia-Martin et al. [15], Paquet et al. [11], Polo et al. [6]). Statistically significant reductions in the overall, superior, inferior, temporal, and nasal RNFL thickness remained. Heterogeneity was reduced but still present within the subgroup and sensitivity analyses, therefore the random-effect model was used allowing for heterogeneity. Funnel plots did not show any correlation between the study size and effect size.

3.2. RNFL thickness in MCI patients compared with controls

We identified five studies including 214 MCI eyes and 421 control eyes, demonstrating a significant reduction in the overall mean RNFL thickness in patients with MCI (WMD −8.23, 95% CI [−14.00, −2.45], P =.005) (Table 3, Fig. 2). There were four studies including 168 MCI eyes and 391 control eyes for the mean RNFL thickness by quadrant, showing significant reduction in all four quadrants; superior (WMD −11.72, 95% CI [−22.59, −0.85], P =.03); inferior (WMD −11.45, 95% CI [−21.00, −1.90], P =.02); temporal (WMD −6.47, 95% CI [−10.74, −2.20], P =.003); and nasal (WMD −4.34, 95% CI [−8.50, −0.19], P =.04) (Table 4, Appendix B). There was significant heterogeneity between the studies, with values of heterogeneity for overall mean RNFL thickness of tau^2 40.61, chi^2 91.67, df 4 (P <.00001), and I^2 96%. Therefore, we performed subgroup analysis according to the type of OCT used (Appendix C). There were three TD-OCT studies and two SD-OCT studies for the overall mean RNFL thickness and two studies each for the RNFL thickness by quadrant. Only the TD-OCT studies showed a significant reduction in the overall, inferior, temporal, and nasal RNFL thickness, whereas the SD-OCT studies only showed a significant reduction in the superior RNFL thickness. Heterogeneity became nonsignificant within the TD-OCT studies for the inferior, temporal, and nasal quadrants, and within the SD-OCT studies for the overall, superior, inferior, and nasal quadrants. A sensitivity analysis excluding Ascaso et al. [9] (where the required data had to be calculated) only showed a significant reduction in the superior and temporal RNFL thickness, with no significant reduction in the overall, inferior, and nasal RNFL thickness.

4. Discussion

The measurement of RNFL thickness using OCT appears to be a promising method to aid in the diagnosis of various neurodegenerative diseases, including AD. Many studies have reported a significant decrease in the mean overall RNFL thickness in patients with AD [5–13], and some have reported significant reductions in the individual quadrants. The superior [5,6,9,12–14,26] and inferior quadrants [5,6,8–10,12,13,26] demonstrating the greatest thinning in patients with AD compared with HC in most studies, whereas the nasal [5,8,9,12,13,26] and temporal [5,9,13,26] quadrants are only found to be significantly thinner in few studies.

Table 2
AD vs normal controls: RNFL thickness by quadrant

	Superior		Inferior		Temporal		Nasal	
Study	AD	Controls	AD	Controls	AD	Controls	AD	Controls
Ascaso et al. [9]	76.58 ± 21.90***	127.4 ± 14.0	85.47 ± 25.70***	134.2 ± 15.57	56.47 ± 15.86***	75.34 ± 15.05	44.59 ± 21.67***	76.84 ± 15.0
Berisha et al. [14]	92.2 ± 21.6*	113.6 ± 10.8	117.0 ± 15.3	128.1 ± 11.4	67.0 ± 15.0	69.5 ± 11.1	65.7 ± 15.1	64.1 ± 7.3
Chi et al. [19]	115.09 ± 14.05*	127.94 ± 12.29	120.64 ± 17.99	129.56 ± 15.17	72.36 ± 17.85	74.69 ± 11.72	65.81 ± 13.02	65.31 ± 8.99
Garcia-Martin et al. [15]	101.4 ± 16.5	102.2 ± 10.8	110.8 ± 11.1	111.8 ± 10.8	71.8 ± 12.5	70.6 ± 11.6	70.5 ± 12.8	72.3 ± 10.6
Gharbiya et al. [20]	114.9 ± 13.8	116.3 ± 14.5	126.9 ± 12.7	124.0 ± 13.6	72.6 ± 14.9	69.8 ± 13.9	74.9 ± 11.5	73.7 ± 12.2
Günes et al. [5]	104 ± 14.2***	126.5 ± 14.0	101.3 ± 16.2***	135.9 ± 16.3	66.6 ± 15.0***	80.2 ± 16.7	67.7 ± 17.0***	85.4 ± 13.5
Iseri et al. [12]	112.64 ± 35.32**	137.16 ± 16.48	103.10 ± 33.64***	141.56 ± 19.09	64.92 ± 17.70	72.30 ± 16.42	63.57 ± 19.09***	96.00 ± 34.39
Kang et al. [8]	103.8 ± 26.71	113.5 ± 20.75	104.8 ± 24.97*	126.1 ± 19.34	58.38 ± 13.24	61.50 ± 10.71	55.31 ± 12.61**	68.81 ± 11.35
Kesler et al. [10]	99.0 ± 18.0*	110.0 ± 16.7	110.1 ± 19.1*	127.0 ± 15.5	61.7 ± 10.9	67.8 ± 15.1	66.8 ± 14.5	76.4 ± 21.8
Kirbas et al. [7]	76 ± 6.7***	105 ± 4.8	106 ± 11.5	108 ± 8.7	74 ± 6.7	77 ± 7.3	75 ± 2.8	76 ± 2.7
Larrosa et al. [22]	113.22 ± 18.67**	117.81 ± 19.00	120.44 ± 20.98***	127.38 ± 20.99	64.47 ± 21.76*	67.83 ± 20.01	72.67 ± 17.31	74.55 ± 17.26
Parisi et al. [13]	72.1 ± 21.4**	104.6 ± 12.1	77.9 ± 26.4**	116.2 ± 9.87	37.9 ± 17.60**	85.6 ± 8.21	50.4 ± 23.2**	93.4 ± 13.7
Polo et al. [6]	113.59 ± 14.5**	118.58 ± 10.8	121.96 ± 16.9*	127.97 ± 15.9	65.00 ± 10.2	66.96 ± 9.2	71.61 ± 15.0	72.12 ± 14.5
Zhu et al. [24]	110.9 ± 27.4**	125.2 ± 20.6	122.1 ± 19.9	131.4 ± 20.1	62.1 ± 19.5***	84.3 ± 13.8	67.9 ± 9.2	67.1 ± 14.0

Abbreviations: AD, Alzheimer's disease; RNFL, retinal nerve fiber layer.
NOTE. *$P < .05$, **$P < .01$, ***$P < .001$ for RNFL thickness in AD compared with controls as reported by the studies.

RNFL thinning has also been reported in patients with MCI [9–11]. Ascaso et al. [9] determined overall RNFL thickness and RNFL thickness in all quadrants to be significantly thinner in patients with amnestic type MCI compared with controls, and conversely to be significantly thicker in patients with MCI compared with patients with AD. However, Kesler et al. [10] report a significant difference between patients with MCI and patients with AD only in the overall RNFL thickness and in the inferior quadrant.

The correlation between clinical severity of AD and overall RNFL thickness is not well established. Although some studies report a significant association between Mini-Mental State Examination scores (MMSE) and RNFL thickness [9], most articles analyzed in this systematic review found no significant difference [5,7,10,13,14]. Iseri et al. [12] reported a strong correlation between the macular volume and MMSE scores, but not RNFL thickness.

Detection of RNFL thinning may also be of prognostic benefit; one prospective case control study reported the ability of OCT measurement of RNFL thickness to predict the risk of cognitive decline in healthy patients [27]. Further studies are, however, required before firm conclusions about OCTs role in prognostication can be made.

Two different generations of OCT technology have been used in the articles analyzed in this systematic review: time-domain OCT (TD-OCT) and spectral-domain OCT (SD-OCT) (also known as Fourier domain). SD-OCT is the more recent technology, and shows considerable improvements over TD-OCT in every aspect of image acquisition, processing, and analysis [3]. The image resolution is improved from 10 to 4 μm, and the speed of acquisition is dramatically improved from around 400 A-scans/second to 40,000/second. Studies using these two generations of technology cannot therefore be directly compared; however, in the articles analyzed within this systematic review, RNFL thinning in patients with AD can be detected on any OCT machine, whether TD-OCT or SD-OCT.

All the studies analyzed had age-matched controls with no significant difference in age between the patients with AD, MCI, and HC, with the exception of Iseri et al. [12]. Age-matching is highly important for the analysis of RNFL thickness, as the RNFL is known to become thinner with natural ageing in HC [27]. Each study excluded patients with any other eye pathology, such as glaucoma and diabetic retinopathy, to prevent ophthalmological comorbidities from having a confounding effect.

The studies analyzed in this systematic review suggest that the significant thinning of the RNFL does occur in AD, and that OCT can be successfully used to detect these changes. A previous meta-analysis [28] of seven different articles studying the RNFL thickness in AD compared with controls, all of which used TD-OCT, determined that there is a significant reduction in RNFL thickness in AD patients compared with HC, overall and in all four individual quadrants. However, the previous meta-analysis grouped patients with AD and MCI together for analysis,

Table 3
MCI vs normal controls: overall RNFL thickness

Study	OCT type	One or both eyes	Number of subjects (eyes)		Mean age ± SD (yrs)		Overall mean RNFL thickness ± SD (μm)	
			MCI	Controls	MCI	Controls	MCI	Controls
Ascaso et al. [9]	TD	Both	18 (36)	41 (82)	AD and MCI: 72.1 ± 8.7	72.9 ± 7.9	86.7 ± 7.18***	103.1 ± 8.04
Kesler et al. [10]	TD	Mix	24 (40)	24 (38)	71.0 ± 10.0	70.9 ± 9.2	85.8 ± 10.0*	94.3 ± 11.3
Paquet et al. [11]	TD	Both	23 (46)	15 (30)	78.7 ± 6.2	75.5 ± 5.1	89.3 ± 2.7***	102.2 ± 1.8
Shen et al. [25]	SD	Mix	23 (45)	52 (104)	74.4 ± 3.2	74.1 ± 2.6	82.6 ± 10.5	85.6 ± 10.2
Zhu et al. [24]	SD	NR	47 (NR)	167 (NR)	76.1 ± 8.2	75.5 ± 7.7	96.8 ± 9.9***	96.7 ± 9.6

Abbreviations: MCI, mild cognitive impairment; RNFL, retinal nerve fiber layer; OCT, optical coherence tomography; SD, standard deviation; TD, time-domain; SD, spectral domain; NR, not reported.

NOTE. One or both eyes or a mix of one and both eyes used per subject in the evaluation of mean RNFL thickness. Number of subjects (number of eyes in brackets).

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

and at least one study has demonstrated that there is a significant difference in RNFL thickness between patients with MCI and those with AD [9]. This study has the advantage of analyzing patients with MCI and patients with AD separately, and also provides an updated review of the literature, which is required after the explosion of studies in this area in recent years. This article includes six new articles and a total of 381 eyes of patients with AD and 84 eyes of patients with MCI compared with 187 patient eyes in the previous systematic review. Additionally, the technology of OCT has advanced and our meta-analysis includes studies using the higher resolution SD-OCT, lacking from the previous review [28].

There are, however, a number of important limitations which must be considered. No studies included the histopathological confirmation of diagnosis; clinical diagnostic criteria in recent use for AD often fail to robustly differentiate accurately between AD and non-AD pathology with up to 40% of patients diagnosed with non-AD dementias identified as having pathology consistent with AD at postmortem in some series [29]. Furthermore, all studies included were cross-sectional; no conclusions can therefore be drawn regarding the timing of RNFL thinning, or of change over time (including any changes detectable at the preclinical stages of dementia). The screening of controls for cognitive symptoms was also not reported by any study, nor did any undertake bedside cognitive testing, biomarker or functional imaging studies (such as amyloid PET) on controls. It may therefore be speculated that the control group may have included those with preclinical dementia, thereby lowering the estimates of differences between groups. Estimates of differences are also potentially limited by the small and underpowered size of most of the studies included.

Finally, one of the aims of this study was to establish the clinical utility of OCT in differentiating between dementia subtypes (such as AD and FTD), unfortunately no studies examining the use of OCT in any other forms of dementia beyond AD met the inclusion criteria. This important question therefore remains unanswered for other common syndromes such as FTD, DLB, and VaD. There is also no consensus yet in the current literature as to the cut-off value or the type of RNFL thickness (overall or individual quadrants) which would best distinguish between AD/MCI and controls, thus precluding the use of sensitivity and specificity which requires a binary classification. Therefore, although this study showed a significant reduction in RNFL thickness in AD compared with controls, this does not directly translate to a measurement of diagnostic utility (sensitivity and

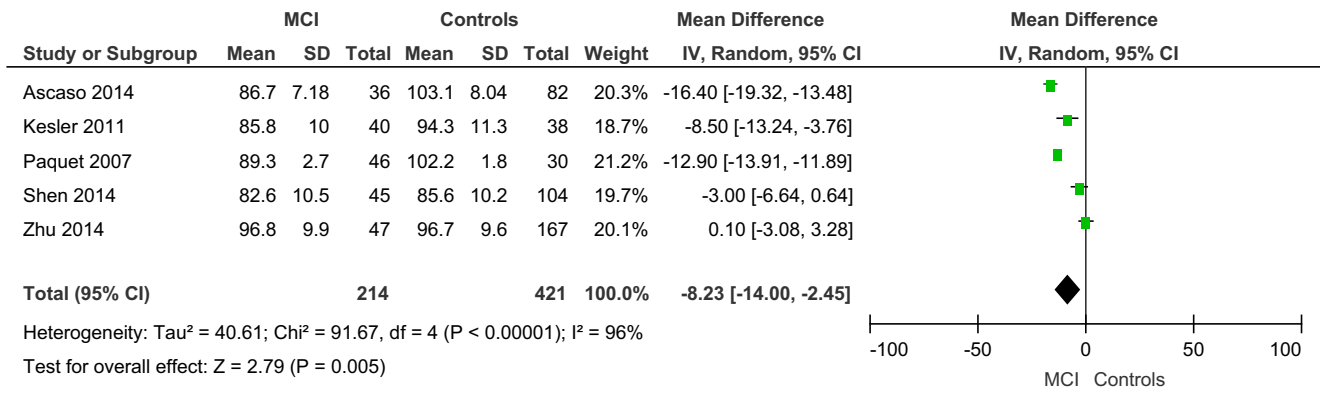

Fig. 2. Meta-analysis of mild cognitive impairment (MCI) vs. normal controls: overall retinal nerve fiber layer (RNFL) thickness.

Table 4
MCI vs. normal controls: RNFL thickness by quadrant

	Superior		Inferior		Temporal		Nasal	
Study	MCI	Controls	MCI	Controls	MCI	Controls	MCI	Controls
Ascaso et al. [9]	100.3 ± 15.5***	127.4 ± 14.0	110.6 ± 18.1***	134.2 ± 15.57	67.38 ± 14.32***	75.34 ± 15.05	68.43 ± 17.16***	76.84 ± 15.0
Kesler et al. [10]	101.3 ± 15.2	110.0 ± 16.7	111.9 ± 16.1*	127.0 ± 15.5	64.2 ± 13.9	67.8 ± 15.1	65.9 ± 15.1	76.4 ± 21.8
Shen et al. [25]	101.8 ± 16.8	104.7 ± 15.4	104.5 ± 17.6	109.3 ± 21.3	62.7 ± 12.2	65.5 ± 10.1	61.5 ± 8.1	64.8 ± 8.4
Zhu et al. [24]	117.1 ± 18.3**	125.2 ± 20.6	128.7 ± 17.2	131.4 ± 20.1	73.1 ± 13.5***	84.3 ± 13.8	67.6 ± 12.2	67.1 ± 14.0

Abbreviations: MCI, mild cognitive impairment; RNFL, retinal nerve fiber layer.
NOTE. *$P < .05$, **$P < .01$, ***$P < .001$ for RNFL thickness in MCI compared with controls as reported by the studies.

specificity), and a further meta-analysis is warranted for this after consensus on the appropriate criteria.

With the rapid pace of advances in OCT technology, we will soon see even greater resolution and detail in the retina. In addition, software improvements are already enabling automated segmentation and measurement of other inner retinal layers, such as the ganglion cell body layer. This may provide additional insights into the pathology of these neurodegenerative conditions. However, the true value and significance of OCT measures of neuroretinal integrity may lie in its integration with other retinal metrics (such as retinal vessel morphology), as part of multimodal retinal imaging. The retinal vasculature is a well-established proxy of both systemic and cerebral microvascular health [30,31] with changes in retinal vascular calibre previously reported in association with cognitive decline. Wider retinal venules are associated with an increased risk of vascular dementia [32], whereas narrower and less tortuous venules have been measured in patients with AD [33,34]. The potential exists therefore for detailed and integrated retinal image analysis to provide meaningful information about our brain in health and disease.

5. Conclusions

The measurement of mean overall RNFL thickness using OCT appears to have the most potential diagnostic utility in the diagnosis of AD. Measurement of the thickness of individual RNFL quadrants may also be of benefit, although results varied. OCT also appears to have diagnostic utility in MCI.

Further investigations are required to fully understand the pathological processes behind RNFL thinning in AD and MCI and the extent to which RNFL thinning is associated with disease severity. Correlation with more sensitive and specific cognitive tests, such as Addenbrooke's Cognitive Examination-III, formal neuropsychological evaluation, and other biomarkers of dementia including imaging and cerebrospinal fluid, has the potential to improve diagnostic accuracy in the absence of histopathology.

Future, larger studies with predetermined power calculations and longitudinal data are required to investigate the change in RNFL thickness over time to determine the use of OCT as a potential surrogate marker in the prognostication of those with MCI. The inclusion of patients with other forms of dementia is also vital to allow the understanding of RNFL disease specificity. Both of these areas are necessary before concluding the true clinical utility of OCT in dementia.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2015.03.001.

RESEARCH IN CONTEXT

1. Systematic review: We searched Medical Literature Analysis and Retrieval System Online, Excerpta Medica Database, Web of Knowledge, Scopus, and Google Scholar for all human studies published in any language to September 2014. We systematically evaluated studies included using the Excerpta Medica Database Quality Assessment for Diagnostic Accuracy Studies checklist and performed meta-analysis of pooled results.
2. Interpretation: This is the most comprehensive systematic review and meta-analysis of retinal nerve fiber layer (RNFL) thickness measurement using optical coherence tomography in dementia to date. Significant differences in pooled results were identified comparing both patients with Alzheimer's disease and mild cognitive impairment with healthy controls, suggesting diagnostic utility.
3. Future directions: There is a need for further well-powered prospective longitudinal studies of RNFL measurement in different dementias, ideally with post-mortem histopathology as a diagnostic gold standard. Future work should also focus on the diagnostic and prognostic value of combined measurements of RNFL thickness and retinal vasculature, potentially using a multimodal approach with other clinical measures and biomarkers.

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